Microsponges: a futuristic approach for oral drug delivery

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Introduction: Microparticulate drug delivery systems have, due to their advantages, guided researchers across the globe to explore them as drug carriers. This has, sequentially, led to the development of microsponges in 1988. These porous microspheres were exclusively designed for chronotherapeutic topical drug delivery but attempts to utilize them for oral, pulmonary and parenteral drug delivery were also made. Researchers have extensively studied their properties and characteristics affecting the drug release and loading. Various advances were made with this carrier particle resulting in the development of various novel development techniques and carrier particles.

Areas covered: This review deals with the considerations of the drug material to be entrapped in microsponges, pharmaceutical considerations for fabrication of microsponges, their potential for oral drug delivery, clinical perspectives and also provides an insight on the recent advances made in this field and future prospect.

Expert opinion: Clinical studies show that these carriers can increase drug efficacy. Due to their potential advantages over other carrier particles, microsponges form a prospective platform for the oral delivery of pharmaceuticals and biopharmaceuticals. Although these carriers have several advantages, they too possess some drawbacks which limit their commercialization for oral application.

Keywords: chronotherapeutic drug release, microsponge, oral drug delivery system, porous structure, resiliency

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1. Introduction

Oral administration of conventional dosage forms normally releases active agent in the gastrointestinal fluid and absorption from the various regions of the gastrointestinal tract (GIT) depend on the physicochemical properties of the drug. The gigantic preponderance of commercially available pharmaceutical formulations comprises immediate-release products that may result in insufficient absorption of the active agent or the compound being cleared from the body before the next scheduled dose. Thus, these formulations may leave the consumers without the therapeutic benefit of the active agent [1]. Controlled drug delivery systems can ameliorate these issues by reducing the dosing frequency, allowing gastric bypass or site-specific delivery, increasing the efficacy of the active compound and improving safety through a reduction in side effects and breakthrough symptoms [2]. The drug delivery technology landscape has become highly competitive and rapidly evolving. More and more developments in delivery systems are being integrated to optimize the efficacy and cost-effectiveness of the therapy. These attempts for development of novel drug carrier systems led to the development of microparticulate drug carrier approach.

Multiparticulate systems form the simplest mode for controlled drug delivery as these systems can control the drug release in various ways like rate control or site control or both and are easy to formulate. Multiparticulate systems are supposed to be more uniformly dispersed throughout the absorption site; thus ensure more homogeneous

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Article highlights.

- The microsponge delivery system (MDS) is also known as solid phase porous microsphere and provide large porous surface for efficient drug loading.
- Liquid–liquid suspension polymerization technique is based on free radical suspension polymerization. The quasi-emulsion droplets of the polymeric solution of the drug solidify in the aqueous phase via counter diffusions of organic solvent and aqueous phase.
- Drug loading on the microsponges depend on physicochemical properties of the active ingredient. Temperature and the solvent system for the inner phase affects the surface morphology.
- Microsponges have the ability to increase the drug release rate due to their porous structure and the mode of drug entrapment. These carrier particles showing matrix type of drug release follow Higuchi model.
- Various studies were carried out to study their potential for oral drug delivery for colon targeting.
- Microsponges offer improved compressibility and produce mechanically strong tablet owing to the plastic deformation of sponge-like structure.
- Microsponges have been successfully studied for colon targeting and their compressed tablets can be used for the chronic purposes.
- Microsponge particles bind to the rough surface of the intestinal mucosa thus provide the efficient local drug delivery.
- Method for preparation of microsponges can be easily modified to use a range of polymers and various advanced carrier systems have been developed by modifying the process of microsponge preparation.

This box summarizes key points contained in the article.

drug absorption [3]. Microparticles also generate an approach for chronotherapeutic drug delivery. Various types of microparticulate systems were developed and studied for this purpose like microspheres [4], microbeads [5], microcapsules [6], microballoons [7] and microsponges. Microsponges due to their various advantages like ease of fabrication, better drug loading and rate control over other microparticulate systems formed the widely studied carrier particle.

The present review is designed to provide detailed information regarding microsponges and their oral application. In addition to this information, the article aimed to provide a brief description of various novel techniques for the preparation of microsponges, various considerations which require to be made before designing microsponges for an active agent, their advantages over other microparticulate delivery systems and the related developments that may enhance the future applicability of the porous carriers.

1.1 Microsponges

The fundamental appeal of the microsponge technology stems from the difficulty experienced with conventional formulations in releasing active ingredients over an extended period of time. The microsponge technology was developed by Won in 1987 and the original patents were assigned to Advanced Polymer Systems, Inc. (Redwood City, California, US). Microsponge technology was introduced for topical drug products to facilitate the controlled release of active drug into the skin in order to reduce systemic exposure and minimize local cutaneous reactions to active drugs.

Microsponge delivery system (MDS), also known as solid phase porous microsphere (**Figure 1**) [8] is a patented microparticulate system, comprising highly cross-linked, polymeric porous microspheres having numerous interconnected voids in the particle, loaded with active agent [9] within a collapsible structure [10] with large porous surface to entrap wide range of active agents with varying pharmacological activities administered in different doses that can be released at the desired site of absorption [11]. The pores in the microparticle form a continuous arrangement open to the exterior surface of particles which permits the outward diffusion of the entrapped drug molecule at a controlled rate depending on the pore size [12]. The high degree of polymeric cross-linking in these microparticles results in insoluble, inert particles with satisfactory strength to stand up to the high shear. These microparticles were once supposed to consist of several nanoparticles under a porous polymeric outer surface [13]. A microsponge of size range 25 µm can have up to 3000 mm/g of pore length with a pore volume of about 1 ml/g. These microparticles have the capacity to adsorb on its surface and or load into the bulk of the particle, high quantities of active ingredient. In addition to efficient entrapment of active ingredients, microsponge technology is believed to contribute toward reduced side effects [14], improved stability, increased elegance [9] and enhanced formulation flexibility. Consequently, this carrier system has been commercially utilized not only for chronotherapeutic topical drug delivery but has also been studied for oral, pulmonary and parenteral drug delivery. In the oral drug delivery, arena microsponges were widely explored for colon targeting drug delivery system [15]. Though this carrier system has a range of advantages over other microparticulate systems, its commercial application for oral drug delivery is still in infancy.

1.2 Marketed products of microsponges

Various products consisting of microsponges are commercialized for topical purposes and systematic research and pilot plant scale-up issues need to be addressed before these can be utilized for oral drug delivery systems. A section of marketed products constituting microsponges of active ingredient are listed in **Table 1**.

2. Preparation of microsponges

2.1 Methods of preparation

Kawashima *et al.*, in 1998 described the method for the preparation of highly porous matrix-type microspheres [16]. In general, the microsponges are prepared by two methods that is, liquid–liquid suspension polymerization and quasi-emulsion

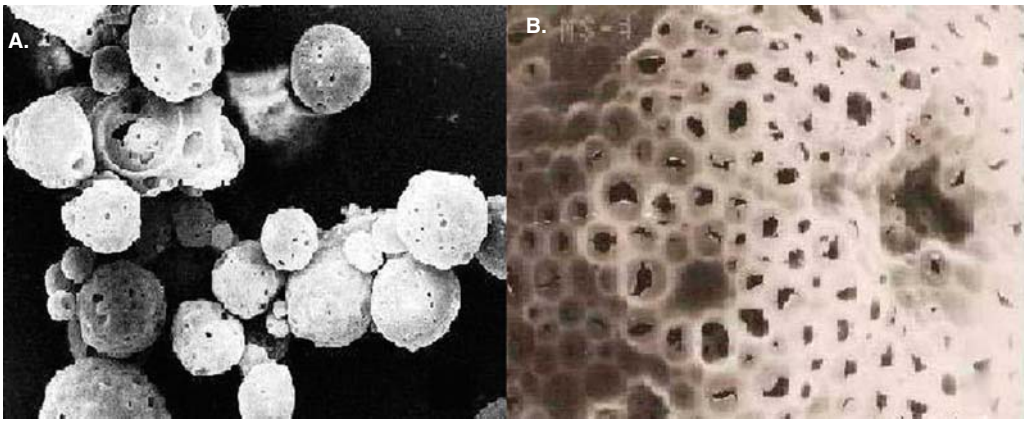

Figure 1. SEM of microsponges. A. Particle view. B. Surface view.

Table 1. Marketed preparations based on microsponge drug delivery system.

Brand name	Drug	Manufacturer
Carac™	5-FU	Dermic Labs, Inc., US
Retin-A Micro®	Tretinoin	A.P. Pharma, Inc., US
Melanin Microsponge®	Melanin	Advanced Polymer System Inc., US
NeoBenz®	BPO	Skin Media, Inc., US
Line Eliminator Dual Retinol Facial Treatment	Retinol	Avon, New York, US
Retinol cream	Retinol	Biomedic
Retinol 15 Nightcream	Retinol	Sothys, Paris, France.
EpiQuin Micro	Hydroquinone and retinol	SkinMedica, Inc., New York, US
Sportscream RS and XS		Embil Pharmaceutical Co., Ltd., Istanbul, Turkey
Ultra Guard	Dimethicone	Scott Paper Co.,Pennsylvania, US
Lactrex™ 12% Moisturizing Cream	Ammonium lactate	SDR Pharmaceuticals, Inc., Andover, NJ, US

BPO: Benzoyl peroxide; 5-FU: 5-fluorouracil.

solvent diffusion, but some novel techniques were recently developed. A brief outline of the all the methods described in the literature are presented in the following sections.

2.1.1 *Liquid–liquid suspension polymerization*

Liquid–liquid suspension polymerization is based on free radical suspension polymerization technique. In the method reported by Grochowicz *et al.*, the reaction was carried out in a round bottom three necked flask fitted with a stirrer, a water condenser and a thermometer (**Figure 2**). A solution of non-polar drug and the monomer(s) was prepared, to which aqueous phase containing surfactant and dispersant was added. Polymerization was initiated by activating the monomers by catalysis or increased temperature or adding an initiator. Water insoluble pore forming diluents may also be added to the reaction mixture [17]. When the drug is sensitive to the polymerization conditions, two-step process can be used [18].

Polymerization leads to the formation of ladders as a result of cross-linking between chain monomers. Folding of monomer ladder lead to the formation of spherical particles and their agglomeration resulted in formation of bunches of microspheres. Binding of these bunches formed microsponge. After polymerization the liquid is diffused out leaving microsponges. Though a convenient method, major disadvantage of this process is probable entrapment of unreacted monomeric residues.

2.1.2 *Quasi-emulsion solvent diffusion*

This process involved formation of quasi-emulsion of two different phases similar to emulsions. The internal phase of drug–polymer solution made in a volatile solvent like ethanol or acetone was added to external phase comprising the aqueous polyvinyl alcohol (PVA) solution with vigorous stirring. Stirring lead to the formation of emulsion globules called quasi-emulsion globules. Solvent was then extracted out from these globules to form insoluble microparticles. Following sufficient stirring, the mixture was then filtered to separate the microsponges (**Figure 3**). The microsponges were then dried in an air heated oven [19]. Conceptually, the finely dispersed droplets of the polymeric solution of the drug (dispersed phase) get solidified in aqueous phase via counter diffusion of organic solvent and water out of and into the droplets [19]. The diffused aqueous phase within the droplets decreased the drug and polymer solubility resulting in the

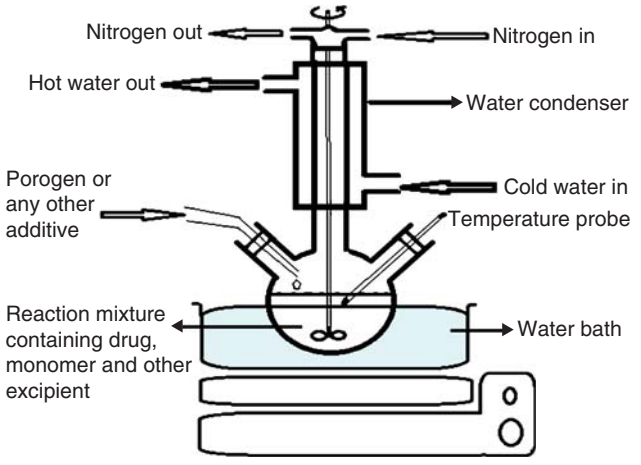

Figure 2. Reaction vessel for microsponge preparation by liquid–liquid suspension polymerization.

co-precipitation of both the components and continued diffusion of the organic phase results in further solidification, producing matrix-type porous microspheres. In comparison with liquid–liquid suspension polymerization method, this method offered the advantage of less exposure of the drug to the ambient conditions, low solvent residues in the product because the solvent get extracted out due to its solubility in aqueous media or due to its volatile nature.

2.1.3 *Water in oil in water (w/o/w) emulsion solvent diffusion*

This novel technique was developed to prepare biodegradable porous microspheres. In this method, an internal aqueous phase containing an emulsifying agent like span, polyethyleneimine and stearylamine was dispersed in organic polymeric solution. Thereafter, this w/o emulsion was again dispersed in external aqueous phase containing PVA to form a double emulsion. This method has the advantage of entrapping both water-soluble or water-insoluble drugs. It can also be used for entrapping thermolabile materials like proteins [20]. Some authors also described the xanthan gum as emulsifier to stabilize the internal w/o emulsion [21].

2.1.4 *Addition of porogen*

In this technique, internal aqueous phase of water in oil in water (w/o/w) emulsion was replaced by a porogen-like hydrogen peroxide or sodium bicarbonate. For this, the porogen was dispersed in the polymeric solution to form a uniform dispersion system which was redispersed in aqueous phase containing PVA. An initiator was then added to the w/o/w emulsion and the organic solvent was allowed to evaporate to leave the microparticles. The effect of incorporating hydrogen peroxide resulted in the formation of evenly distributed and interconnected pores with diameters ranging from 5 to 20 μm [22].

2.1.5 *Oil in oil emulsion solvent diffusion*

In contrast to w/o/w method, oil in oil (o/o) emulsion was prepared using volatile organic liquid as the internal phase that was allowed to evaporate slowly at a controlled rate with continuous stirring. As reported the technique used dichloromethane as the solvent for internal phase, polylactide glycolic acid as polymer and a mixture of fixed oil (corn or mineral) and dichloromethane containing span 85 as external phase. The internal phase was added drop wise to the dispersion medium with continuous stirring to get the microsponges [23]. This technique was utilized for development of hydroxyzine HCl-loaded Eudragit RS-100 microsponges using acetone as dispersing solvent and liquid paraffin as the continuous medium [24]. Selection of the organic solvent and external phase depend on the physicochemical properties of drug and the polymer used for fabrication of microsponges.

2.1.6 *Lyophilization*

Lyophilization as technique was used for converting the microspheres prepared by gelation technique, to porous microspheres. In this methodology, the microspheres were incubated in the solution of chitosan hydrochloride and then lyophilized [25]. Quick removal of solvent led to formation of pores in the micropheres. This method is quick and rapid but has the disadvantage of producing cracked or shrunken microparticles due to quick elimination of solvent.

2.1.7 *Vibrating orifice aerosol generator method*

Vibrating orifice aerosol generator (VOAG) was first reported for the preparation of lipid bilayered mesoporous silica particles. The method involved synthesis of porous particles by evaporation-driven surfactant templating in microdroplets by a VOAG method. For the preparation of core particle tetraethylorthosilicate, ethanol, water and dilute hydrochloric acid were refluxed to prepare stock solution. This stock solution was diluted with the solvent containing surfactant and stirred to allow the formation of monodisperse droplets using VOAG [26]. The microspheres produced were encapsulated in the liposomes. These encapsulated particles can be utilized for targeted drug delivery of actives.

2.1.8 *Ultrasound-assisted production*

This method was developed by modifying the liquid–liquid suspension polymerization, to utilize β-cyclodextrin (β-CD) as monomer and diphenyl carbonate as cross-linking agent to synthesize the nanosponges. Size control of the microparticles was accomplished by heating and sonication of the reaction mixture. The reaction mixture was allowed to cool and the product obtained was milled to give rough particles that were washed with distilled water and then by ethanol [27]. The porous microparticles of cross-linked β-CD can serve as carrier for efficient loading of drugs. However, this method has the disadvantage of entrapment of residues of the cross-linking agents that can be potentially toxic.

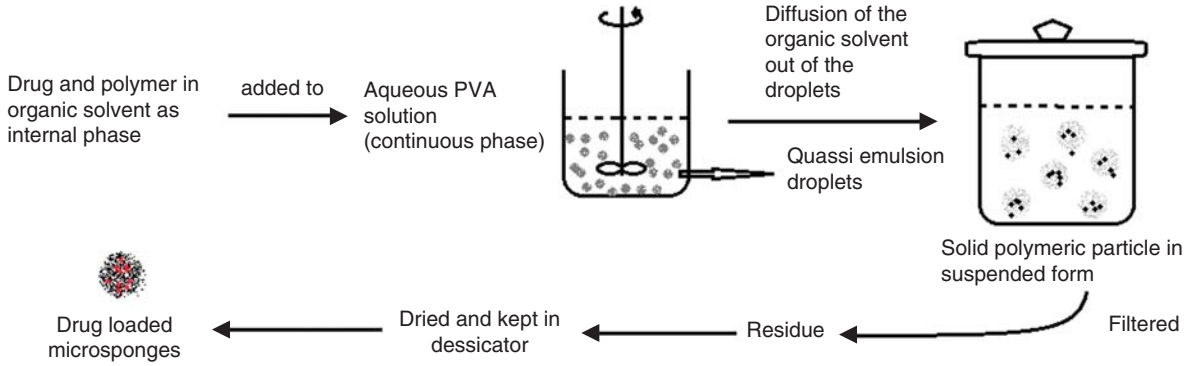

Figure 3. Preparation of microsponges by quasi-emulsion solvent diffusion method.

2.1.9 Electrohydrodynamic atomization method

This method was employed to produce porous microspheres of chitosan by Pancholi *et al.*, in 2009. Chitosan solution was sonicated to generate bubbles and the resultant bubble suspension was drawn into a syringe, perfused through a steel capillary using a syringe pump and finally subjected to electrohydrodynamic atomization. The diameter of the capillary was chosen to retain all bubbles in the suspension while it flowed through it. The voltage used in the experiments solely depends on the concentration of chitosan in the solution. The combination of flow rate and applied voltage resulted in the stable cone-jet mode in each case, except when highest concentration was used that was difficult to electrospray. The chitosan microspheres were cross-linked by 4% w/v sodium hydroxide aqueous solution [28].

Though various methods have been reported for fabrication of microsponges, each of them has its own advantages and disadvantages. **Table 2** compiles these issues.

2.2 Polymers and formulation aids in microsponges

Various polymers were reported to form microsponge 'cage'. Polymers studied for the fabrication of microsponges for the oral purposes include Eudragit RS-100, Eudragit RS PO, Eudragit S-100, polylactide-co-glycolic acid, polylactic acid, polydivinyl benzene and polyhydroxyl butyrate. Eudragit RS-100 formed the most widely studied polymer due to its versatility enabling the researchers to employ it in various ways. It was mostly exploited for the development of colon-targeted microsponges due to its high transition pH (above 7) which enabled to protect the release in lower pH. Eudragit RS PO also modulated the drug release along with enhancing the solubility of the drug by forming a solid dispersion-like structure. Polylactide-co-glycolic acid and polylactic acid were studied for delivering the proteins and peptides. Microsponges fabricated with these polymers also possessed floating ability due to the hydrophobicity of the polymer which limited the wetting of the particles with aqueous media, thus these microparticles can be employed for fabricating floating microsponges. Polydivinyl benzene was studied for fabricating the porous microparticles by polymerization technique using divinyl benzene as monomer but entrapping the drug with this process may cause alteration in structure of drug molecule or conjugation of drug with monomer. The use of such a large variety of polymers for the fabrication of the microsponges showed that the method of preparation of microsponges can be modified as per the requirement. In addition to polymers and active ingredients, some researchers also used triethylcitrate as plasticizer that help to stabilize the resilient property of the microsponges [29]. During the preparation of microsponges by quasi-emulsion solvent diffusion method, it is reported that the presence of an emulsifier having tendency to maintain the viscosity of aqueous phase is compulsory [19]. Researchers attempted the use of cellulose ethers and PVA for such role and found the use of PVA as a better emulsifier.

3. Characteristics of microsponges

Microsponge formulations are stable over the range of physiological pH thus can be used as a versatile carrier system. These are thermostable and can withstand temperatures of 130°C. Microsponge formulations are self-sterilizing as the average pore size is 0.25 µm that limits bacterial penetration. Microsponge formulations have high loading efficiency, are free flowing with good compressibility characteristics and are cost-effective carriers for drug delivery. The porous structure of these carriers facilitates the penetration of the dissolution media into the drug-loaded core and thus can be used to enhance the dissolution rate of the poorly soluble drugs. Furthermore, the mode of entrapment of drug by the carrier system leads to the particle size reduction of drug and increases dissolution rate [30]. In case of topical delivery, when compared with the other delivery systems, microsponges can prevent excessive accumulation of active ingredients within the epidermis and the dermis thus can reduce significantly the irritation of effective drugs without reducing their efficacy [31].

Table 2. A compliation of the advantages and disadvantages of various methodologies used for preparation of microsponges.

Method	Advantages	Disadvantages
Liquid–liquid suspension polymerization	Can be suitably modified to one step or two step methods for drug loading	Probable entrapment of unreacted monomers and solvent traces. Non-uniform structure. Requires long time for the reaction of monomers. Requires two-step method for thermosensitive drugs that has low drug loading efficiency
Quasi-emulsion solvent diffusion	No monomer entrapment. Low solvent traces. High drug loading. No exposure of drug to ambient condition. Size of microsponges can be easily controlled by controlling the stirring. Spherical particles	Cannot be used for the loading of water-soluble drugs. Requires long time for the reaction of monomers. Drug should be soluble in a volatile water-soluble solvent
w/o/w emulsion solvent diffusion	Efficient for loading water-soluble drugs. Can be used to entrap proteins and peptides	Uses water-insoluble surfactants that can be present as residues in the resultant microsponges
Addition of porogen	Highly porous structure with nicely distributed and interconnected pores	May cause disruption in structure
o/o emulsion solvent diffusion	No presence of surfactant traces in microsponges	Requires vigorous washing to remove the traces of organic solvents
Lyophilization	Easy quick reproducible results	May lead to cracking or shrinkage of microparticle
VOAG method	Results in microsponges that can be used for targeted drug delivery	Requires reflux conditions
Ultrasound-assisted production	No traces of solvents. Quick reproducible results	Irregular structure. Require cross-linking agents that may be potentially toxic. May lead to the binding of drug molecule to the monomer Control of size of particle and pores requires expertise
Electrohydrodynamic atomization method	Quick reproducible results	

o/o: Oil in oil emulsion; VOAG: Vibrating orifice aerosol generator; w/o/w: Water in oil in water emulsion.

4. Characteristics of materials entrapped in microsponges

Active agents that can be entrapped in microsponges must be either fully miscible in monomer or freely soluble in a water immiscible solvent for liquid–liquid suspension polymerization, while for quasi-emulsion solvent diffusion method, the drug must be water immiscible. In latter case, if the drug is soluble in aqueous media, its entrapment in the carrier will be drastically reduced. Other desirable attributes include stability in the drastic conditions of polymerization and with polymerization catalyst used for microsponge formation [32].

5. Pharmaceutical aspects of microsponges

5.1 Physical attributes of microsponges

5.1.1 Particle size

Microsponges as free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. Particle size has its impact on drug loading and drug release profile. Significant formulation factors that affect particle size include drug:polymer ratio and the concentration of emulsifying agent. An increase in the drug:polymer ratio results in small particles. On the other hand, increasing the concentration of emulsifying agent leads to formation of large-sized microsponges.

5.1.2 Morphology and surface topography

The morphological study of the microsponges by various researchers demonstrated the presence of pores on the surface of the carrier. Surface morphology of the microsponge is influenced by the temperature maintained during the preparation and the selection of solvent system for the inner phase. Any condition or solvent system, causing quick precipitation of polymer results in non-porous or less porous surface [33].

5.1.3 Loading efficiency and production yield

Drug loading in microsponges can be made by two ways, either as passive loading (one-step process) [30] or by active loading (two-step process) [18]; depending on the physicochemical properties of the drug to be loaded. Passive loading seems to be easy, convenient and more efficient

than active loading. Thus, most of the researchers utilize passive drug loading as a method of choice. An increase in the drug:polymer ratio and decrease in the particle size, increases drug loading efficiency and production yield [34].

5.1.4 *True density*

Determination of this parameter helps in determining porous character of the microsponge. Highly porous particles have lower true density as maximum volume is covered by the pores. Such systems have higher release rate but are fragile. While microsponges with higher true density have collapsible structure and permit slower drug release. Such carrier particles are preferred for tabletting as they easily regain their shape on contact with dissolution fluid.

5.1.5 *Rheological properties*

Good rheological properties are required for product development as it helps in better die or capsule filling and compression. Tablets and capsules constitute the most feasible dosage form for the oral use and their formulation require good flow properties of the material to be compressed/encapsulated. As microsponges are spherical, they have good flow properties and their microstructure helps in better compression.

5.1.6 *Resiliency*

Resiliency (viscoelastic properties) of microsponges is used to define the firmness of the final formulation (either soft or firm). This property influences the collapsible characteristic as well as drug release of the microsponges. It is very necessary to optimize the firmness of the microsponges that can be done by optimizing the cross-linking and observing the drug release behavior, but unfortunately no validated and optimized method has been developed to determine the resiliency of microsponges [11].

5.1.7 *Pore structure*

Microsponges prepared by the suspension polymerization method have been reported to have smaller pore size as compared with that of the microsponges prepared by the quasi-emulsion solvent diffusion method, thus the microsponges by former method release drug slowly [35].

5.1.8 *Internal porosity*

The internal porosity of the microsponges can be easily controlled by changing the concentration of the drug and the polymer in the emulsion droplet. At lower concentration of drug, the microspheres with higher porosity are obtained. The internal porosity of microsponges significantly influences the characteristics of microsponges. The drug release profile from these carrier particles best fits Higuchi model that indicates its dependency on the internal porosity. Particles with similar internal texture showed almost same tortuosity irrespective of their surface porosity [36].

5.2 Polymer/Monomer composition

Polymer composition of the MDS can affect partition coefficient of the entrapped drug between the vehicle and the microsponge system and hence provide direct influence on the release rate of drug. Quasi-emulsion solvent diffusion method can be modified to use various polymers in combination for the preparation of microsponges [37]. Various grades of Eudragit like Eudragit RS-100, Eudragit RS PO, etc., and other polymers like polylactic acid, poly-L-glycolic acid, polydivinyl benzene and polyhydroxy butyrate were studied for fabricating the microsponges for oral usage. Various monomers like divinyl benzene and hydroxy butyrate, etc. alone or in combinations were screened for their suitability with the drugs by studying their drug release profile and the vehicle to be used for their dispersion.

5.3 Release evaluation

Drug release studies showed that the microsponges have the ability to increase the drug release rate due to their porous structure. The selection of the dissolution fluid is based on the type of delivery system it is intended to be used. By proper manipulation of the programmable parameters, microsponges can be designed to release the given amount of active ingredients over time in response to one or more external triggers like pressure, temperature change and solubility of active material in dissolution media. Application of high pressure was observed to increase the drug release for topical use thus it can be extrapolated, that presence of food and contractions in the GIT can increase the drug release when used orally. The release can also be activated by diffusion taking into consideration the partition coefficient of the ingredient between the microsponges and the outside system. Microsponges showed matrix type of drug release, that is, following Higuchi model of drug release.

Various factors that are to be considered during development of such formulations include physicochemical properties of entrapped active agent, physical properties of microsponge system like pore diameter, pore volume, resiliency and properties of vehicle in which the microsponges finally disperse [38]. **Table 3** lists some of the evaluation parameters of the microsponges and the method for determination thereof.

5.4 Formulation considerations

When formulating the microsponge, certain considerations are taken into account in order to achieve desired product characteristics. The aqueous solubility of active agent must be limited otherwise the continuous phase will deplete the microsponges during formulation and polymer design and payload of the microsponges for the active must be optimized for required release after given time period.

Kawashima *et al.* prepared microsponges by dissolving the drug and polymer in ethanol by modified emulsion solvent diffusion method. On addition to the aqueous phase, the ethanol diffused from the emulsion droplets to leave a highly

Table 3. Characterization parameters of the microsponges and recommended methods.

Characterization parameter	Methods	Remarks	Ref.
Particle size	Microscopy diffractometry, DLS	The value of the size of 50% can be expressed for all formulations as mean size range	[76]
Morphology and surface topography	SEM	Prepared microsponges are coated with gold–palladium under an argon atmosphere at room temperature and then studied	[63]
Production yield	Weight calculation	$Production\ yield = \frac{Practical\ quantity}{Theoretical\ quantity\ (polymer + drug)} x100$	[77]
True density	Ultra pycnometer	Is done under the helium gas environment	[78]
Rheological properties	Static funnel method, tapping method	Includes bulk density, tapped density, angle of repose, compressibility index, Hausner's ratio and % porosity	[79]
Compressibility	Tapping method	Microsponges have better compression characteristic	[79]
Polymer/monomer composition	Formulation optimization	Various polymers have been studied for microsponge preparation	[37]
Resiliency	Process optimization	No optimized method has been developed to determine the resiliency of the microparticles	[11]
Pore structure	Mercury intrusion porosimetry, gas sorption analysis	Pore volume is determined by using Washburn equation: $D = \frac{-4\gamma\cos\theta}{P}$ Where D is the pore diameter (μm); γ the surface tension of mercury (485 dynes/cm); θ the contact angle (°) and P is the pressure (psig)	[80,81]
Drug content	Drug extraction	These carriers have better drug loading, thus they provide better drug content	
Loading efficiency	Drug extraction	$Loading\ efficiency = \frac{Practical\ drug\ loading\ x100}{Theoretical\ drug\ loading}$	[77]
Drug release study	USP apparatus II	When studied for oral use, the speed of the rotation is 100 rpm; temperature is maintained at 37 ± 0.5°C done at various physiological pH for the stated time period	[82]
Compatibility studies	DSC, X-ray diffraction, FTIR, chromatographic techniques	Is performed as per the guidelines of ICH, WHO and APA	

APA: Association of Pharmaceutical Analysts; DLS: Dynamic light scattering; DSC: Differential scanning calorimetry; FTIR: Fourier transform infrared spectroscopy; ICH: International Conference for Harmonization; SEM: Scanning electron microscope; WHO: World Health Organization.

porous particle. They employed sucrose fatty acid ester as the emulsifying agent. Variation in the ratios of drug and polymer in the ethanol solution provided control over the porosity of the particle. An approach to evaluate the loading capacity of these microsponge delivery systems was based on utilizing the relative inter-particulate friction sensing capability of the Hausner's ratio and comparing it with a more conventional flowability test [16].

Baykara and collaborators formulated the ketoprofen microsponges for the oral use and studied the effect of process variables like mixing speed, drug:polymer ratio, solvent:polymer ratio on the physical characteristics and drug release. They concluded that on increasing the drug:polymer ratio, the particle size of the microsponges decreased. They also noticed that the release of ketoprofen was modified in all formulations following Higuchi model [34]. The researchers made an attempt to explore the utility of the microsponges for oral drug delivery and also studied the effect of pressure for compression for tabletting of ketoprofen microsponges by applying different pressure values to the mass in order to determine the optimum pressure value for compression of the tablets. The microsponges demonstrated better compressibility over the physical mixture of the drug and polymer, owing to the plastic deformation of sponge-like structure and produced mechanically strong tablets [39]. They also proved that tablets comprising microsponges showed improved bioavailability when compared against the commercially available tablets for ketoprofen but these tablets showed delayed drug release and absorption. This led to the conclusion that tabletting of the microsponges increases the lag time for drug appearance in plasma and maintains the drug concentration for longer period [40].

Cui *et al.* designed microsponges for nitrendipine which behaved like solid dispersion, by modifying the quasi-emulsion solvent diffusion method. Hydroxypropyl methyl cellulose (HPMC) phthalate was used as solid dispersion carrier; Eudragit RS-100 and ethyl cellulose as retarding agent and anhydrous silicic acid as dispersing agent. This study showed that increasing the content of carrier and dispersing agent increased the release rate. Oral administration of microsponges in male dogs demonstrated threefold increase in relative bioavailability when compared with conventional dosage form. This study revealed that the procedure for development of microsponges can be tailored as per the requirement of the drug release [41]. Graves *et al.* formulated biodegradable microsponges of polylactide glycolic acid (PLGA) for the delivery of proteins and peptides. They added sodium bicarbonate to form porous structure and found that increasing the amount of bicarbonate resulted in increased porosity and decreased tapped density [42]. In another report, Gao and collaborators prepared porous polylactide microspheres by emulsion solvent evaporation based on solution-induced phase separation. They prepared the internal phase by dissolving the polymer (PLA) in the methylene chloride and then adding *n*-hexane in the prepared polymeric solution. The organic phase was then dispersed in the aqueous phase containing PVA. They revealed that particles with larger pores and floating ability are formed without addition of the non-solvent and concluded that the larger pores reduced the true density of the particles which enabled the porous microspheres to float and these can also be used to develop microsponges-based novel gastro retentive drug delivery systems [33].

6. Advantages and limitations of microsponges over other microparticles

Microsponges have improved thermal, physical and chemical stability over other microparticulate systems [30]. Microsponges provide better entrapment efficiency when compared with other microparticulate systems [43]. Using these carrier systems liquids can be converted into powders leading to improved material processing [44]. Microsponges are flexible for the development of novel dosage forms [15]. The system is free flowing [44] and cost-effective thus can be used at commercial level. A generally accepted view is that multiparticulate systems perform better *in vivo* than single unit systems, as they spread out throughout the GIT causing less irritation, enjoy a slower transit, extended retention and give a more reproducible drug release [45]. Microsponges have shown a better compressibility for tabletting when compared with the other microparticulate systems or the physical mixture of the drug and the polymer [39]. An added benefit is that the time it takes the microsponge system to traverse the small and large intestine is significantly increased thus maximizing the amount of drug that is absorbed. In addition, the entrapment process in the microsponge allow for both co-loading and subsequent loading steps including coatings.

But irrespective of their various advantages, microsponges also suffer from some barriers that limited their applications. These barriers include the uncertainty in the production techniques and no efforts for pilot plant on commercial level. Various methods that were developed for their production are not reproducible. Researches showed the efficacy of microsponges toward protein delivery but after release microsponges cannot protect them from microbial flora at the site of release. Although smaller pores of microsponges limit the entry of microorganisms to the bulk but they can grow on the surface of microsponges [46]. Similarly, the use of biodegradable polymers for the delivery of amino acids and proteins lead to the generation of monomers at the site which may cause harm to the physiology of the human body. Another such barrier includes the development of a suitable dosage form for their targeted delivery. Microsponges can be suitably converted to a colon-targeted tablet by using pectin for compression coating [47] or calcium pectinate as matrix former [15] but these microsponges on their own cannot protect the active ingredient from release in upper part of GIT.

7. Microsponge: as oral delivery system

Microsponges are frequently used for topical delivery [9-11]. Due to their elegance these carrier systems also have applications in cosmetics [11]. MDS were also studied for the peptide delivery

by varying ratio of polymers [20]. These microparticles possess potential for oral administration [48] and pulmonary delivery [49]. Sun *et al.* also investigated the potential of porous microsphere as injectable drug delivery system for controlled protein delivery using human serum albumin as model drug [50]. Giovagnoli *et al.* studied the potential of the porous microspheres of capreomycin sulfate for pulmonary use [49].

Microsponge drug delivery system is suitable for drug delivery through oral route as these have the ability to increase the rate of drug release of poorly water-soluble drugs by entrapping such drugs in the microsponge pore system [48]. Preliminary studies as performed by the A.P. Pharma, Inc., Redwood City, CA, USA indicated that the microsponge particles bind to the rough surface of the intestinal mucosa thus these carrier systems have potential to increase the bioavailability by the combination of the enhanced rate of adsorption and dissolution [51]. A microsponge system offers the potential to hold active ingredients in a protected environment and provide controlled delivery to the lower GIT. The reason for selection of microsponges as colonic delivery system is due to the fact that, drug carrier system has a size less than 200 µm that can be efficiently taken up by the macrophages present in colonic tissue, thus exhibit effective localized drug action at the desired site [52].

To determine if coated microsponges form a viable option for sustained release of chlorpheniramine maleate, drug-loaded cellulose microparticles were coated with Eudragit RS-100 to form powder-coated microsponges. The researchers observed that the powder-coated granules demonstrated lower C_{max} (maximum plasma drug concentration) and longer T_{max} (time for maximum plasma drug concentration) than the powder chlorpheniramine maleate, following oral administration in dogs [30]. Orlu *et al.* made an approach for the colon targeting of flurbiprofen by preparing pectin-coated tablets containing microsponges as core. Additionally, they studied the active drug loading method with commercially available Microsponge® 5640 system determined that active loading in case of microsponges reduced the drug content and encapsulation efficiency while the microsponges prepared by quasi-emulsion solvent diffusion possessed spherical pores with larger diameter. Their study also revealed that very high drug:polymer ratio failed to prepare microsponges while by reducing the drug:polymer ratio highly porous spherical microsponges were obtained. Microsponges on compression gave mechanically strong core tablets which provided sustained drug release. They also prepared colon-specific tablet by pore plugged method using the same polymeric mixture. Tablets prepared by the pore plugged method showed zero-order release kinetics [47].

Devrim and Canefe in 2006 prepared microsponges for the delivery of ibuprofen and also studied the effect of polymers (Eudragit RS-100, Eudragit RS PM and Eudragit RL 100) on various characteristics of the microsponges including rheological properties along with the particle size and release characteristics and concluded that all the microsponges possessed good flow properties, required for the maintenance of the dose and weight uniformity during tablet compression or capsule filling. They also observed that smaller particles with better control over drug release were obtained with Eudragit RS-100 when compared with that formed with other grades of Eudragit [53].

Jain and Singh prepared the dicyclomine-loaded microsponges for colonic delivery by quasi-emulsion solvent diffusion method to study the effect of process variables and analyzed *in vitro* drug release data. This research illustrated that increasing the quantity of emulsifying agent increases the particle size of the microsponges. Another observation related to the drug:polymer ratio showed that increasing the drug:polymer ratio resulted in reduced production yield and smaller particles but increased drug content. The drug release profile of the microsponges showed the best fit for Higuchi model. The researchers also observed that increasing the polymeric content resulted in better control over drug release [54]. The authors had also developed and characterized the paracetamol-loaded colon-targeted drug delivery system employing microsponges by coating with natural polysaccharides like citrus pectin which enabled it to inhibit the drug release for initial 8 h while releasing the drug after adding the enzyme pectinex. This study also revealed the capability of the microsponges to load the drugs which required to be used in the high dose, thus proving that the microsponges have better loading efficiency than other microparticulate (microballoons, microcapsules and microspheres) system. They observed a decrease in drug release rate with the increase in drug:polymer ratio following a biphasic release [55]. The authors performed *in vitro* release studies and observed that the main mechanism of drug release was diffusion [56]. Kadam *et al.* developed microsponge-based drug delivery system for the delivery of aceclofenac and observed that such systems reduced the crystallinity of the drug particles and their compressed tablets can be used for the chronic purposes [57]. Jain *et al.* revealed the capability of Eudragit S-100 for the development of the microsponges for colon targeting [52].

Dhawale *et al.* prepared the %-fluorouracil-loaded porous microspheres and observed that drug release showed generally similar behavior at the different pH. These carriers were efficient enough to retain the drug inside the microspheres during *in vitro* drug release study in simulated gastric and intestinal fluids while a fast release was observed in colonic range, which delivered about 100% of the incorporated drug within 60 min [58]. Srivastava *et al.* developed the microsponges by using sodium chloride as porogen and observed that the use of porogen lead to the uniform porous outer surface with interlinked porous internal structure. They also observed that structural integrity was not lost during drug release but the surface got eroded as a phase transition of surface occurred by the release of drug molecules adsorbed on the surface. Their research showed on compression to a matrix tablet fabricated with microsponges did not cause any disruption in the integrity of microsponges. Their experiment also revealed the surface retentive ability of the microsponges leading to the reduced systemic exposure of the active ingredient [15].

8. Clinical perspective

Due to their clinical superiority over other carrier systems they were approved for the treatment of dermatomycosis, acne and actinic keratosis [59]. Various performed clinical studies suggested that entrapping any active agent in microsponges or nanosponges would increase their efficacy and safety. In such effort hydroquinone and retinol were entrapped in microsponges and studied clinically in an open-label study for the treatment of hyperpigmentation and the developed system was compared against unentrapped drug. The study concluded that the disease severity and pigmentation intensity was statistically improved compared with baseline. Microentrapped drug components were well tolerated, safe and effective [14,60]. In the same perspective while studying the *in vitro* efficacy of such carriers to treat cancer, the study showed that efficacy of tamoxifen [61] and paclitaxel [62] was improved by entrapping them in the nanosponges.

9. Recent advances in microsponge drug delivery system

Various advances were made by modifying the methods to form nanosponges, nanoferrosponges and porous microbeads. Nanosponges were used for the passive targeting of cosmetic agents to the skin, thereby reducing the total dose, avoiding systemic absorption and extended retention of dosage form on the skin [10]. These were developed by modifying various parameters of the quasi-emulsion solvent diffusion method like agitation rate, amount of polymer, amount of emulsifying agent and volume of inner phase and continuous phase. Decreasing the amount of the polymer or increasing the drug:polymer ratio resulted in decreased particle size [63]. β-CD nanosponges were also developed that can be used for hydrophobic as well as hydrophilic drugs, in contrast to polymeric micro or nanosponges [64-66]. These advanced systems were studied for oral administration of dexamethasone, flurbiprofen, doxorubicin hydrochloride, itraconazole and serum albumin as model drug. These nanosponges were developed by cross-linking the β-CD molecule by reacting the β-CD with diphenylcarbonate. The pore size of these cross-linked, nanoporous materials can be modulated by varying the CD/PMA molar ratio. In the presence of aqueous solutions they can show gel-like behavior [64]. β-CD nanosponges were observed to increase the drug release rate of an practically insoluble drug, itraconazole by forming a ternary complex using copovidone [65]. Swellable nanosponges of β-CD were developed by cross-linking β-CD with 2,2-bisacrylamido acetic acid in aqueous solution. Homogenized nanosponges showed stability as these did not undergo aggregation during storage [66]. Some researchers also observed the nanosponges as good carrier for the delivery of gases [67]. Researchers also observed that incorporating a cytotoxic in a nanosponge carrier system can increase the potency of the drug suggesting that these carriers can be potentially used for targeting the cancerous cells [61,62].

Nanoferrosponge, a novel approach constituted the self-pore-forming carriers having better penetration to the targeted site due to the external magnetic trigger which enforces the carriers to penetrate to the deeper tissue and then causing the removal of magnetic material from the particle leaving a porous system. These were prepared by co-precipitating the polymer and magnetite. The ferrosponges showed high swelling ratios, together with excellent elasticity, hydrophilicity and rapid response to an external magnetic stimulation for fast and repeatable swelling–deswelling (or expansion–contractile) operations [68]. Due to the improved characteristics of porous microspheres, process was developed to produce the porous microbeads. This method (high internal phase emulsion, HIPE) consisted of the monomer containing continuous oil phase, cross-linking agent and aqueous internal phase. Polymerization and cross-linking was activated by heating them to convert the liquid HIPE microdroplets to solid microbeads [69].

Some authors also described the addition of magnesium stearate to the dispersed phase to prevent flocculation of the Eudragit RS-100 microsponges when preparing these particles by oil in an oil emulsion solvent diffusion method. Pore inducers such as sucrose and pregelatinized starch were also reported to enhance the rate of drug release [24]. Some researchers also performed the accumulation study with resveratrol-loaded nanosponges in rabbit mucosa and observed that nanosponges have better accumulation than plain drug. These results signify that nanosponges formulation can be used for buccal delivery and topical application [70]. Some other researchers also observed the effect of nanosponge formulations to protect the lactone ring of camptothecin after their incubation in physiological conditions at 37°C for 24 h. Their study showed that nanosponge formulations are able to enhance the stability of the labile drug compounds [71].

Lee *et al.* developed a self-assembled microsponge system for the delivery of short interfering RNA (siRNA). They reported the synthesis of a delivery vehicle that combines carrier and cargo: RNA interference (RNAi) polymers that self-assemble into nanoscale pleated sheets of hairpin RNA, which in turn form sponge-like microspheres consisting entirely of cleavable RNA strands, and are processed by the cell's RNA machinery to convert the stable hairpin RNA to siRNA only after cellular uptake, thus inherently providing protection for siRNA during delivery and transport to the cytoplasm. They also observed an improved stability of RNA and the relatively effective encapsulation process of siRNA. The approach could lead to novel therapeutic routes for siRNA delivery [72]. In an attempt to determine the influence of microsponge formulation on the flux for percutaneous drug delivery, Maiti *et al.* developed diclofenac sodium-loaded ethyl cellulose microsponges-loaded gel through w/o/w emulsion technique. They reported that microsponge formulation reduced the flux of drug across the skin thus can retain the drug at the delivery site. These formulations reduced the drug permeation through skin and maintained the required concentration of drug at the desired site [21].

10. Reported patents on microsponges

Various patents were reported on microsponge drug delivery system but none of them deals with oral drug delivery. Advanced Polymer Systems, Inc. and subsidiaries (APS or the Co.) was using its patented MDS and related proprietary technologies to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter and personal care products like tretinoin, 5-fluorouracil (5-FU) and vitamin A, etc. As on July 2006, the company had a total of 10 issued US patents and an additional 92 issued foreign patents; 21 patent applications were pending worldwide [73]. Dean Jr. *et al.* in 1989 disclosed the preparation of weighted collagen microsponges for immobilizing the microorganisms. This patent was assigned to Verax Corp., Germany. The disclosed invention permitted the continuous growth of the entrapped microbes and was formed of the highly cross-linked collagen [74]. Other such disclosed patent include a microsponge impregnated non-woven towel, assigned to the Millikan and Co (Spartanburg, South Carolina, US) and invented by Love *et al.* in 2008 [46].

A.P. Pharma developed the proprietary technology for oral controlled delivery using porous alginate microspheres as an effective carrier for delivery of hydrophilic molecules in addition to macromolecules, such as vaccines and peptides orally. The company investigated and conducted clinical studies for these carriers as vehicle to deliver agents to the lower GIT, specifically the colon by developing a composite tablet designed with the active agent loaded into the microsponge system. Human proof-of-principle studies demonstrated the ability of the tablet design to bypass degradation in the stomach and small intestine to deliver drugs to the colon thus this system is potentially applicable to a large group of chemically diverse agents for selective delivery to the colon, including laxatives, steroids, amino salicylic acids, etc. Company is trying to deliver corticosteroids by appropriately modifying the microsponge system due to its ability to entrap and release the water-insoluble drugs at rates several times higher than the conventional micronized versions of the drugs [51]. At present, this technology is patented to Cardinal Health, Inc. (Dublin, Ohio, US) for topical use [75].

11. Future prospects

Microsponge drug delivery system holds a promising opportunity in various pharmaceutical applications in the upcoming future as it has unique properties like enhanced product performance and elegancy, extended release, improved drug release profile, reduced irritation, improved physical, chemical and thermal stability which makes it flexible to develop novel product forms. The real challenge of MDS in future is the development of the delivery system for the oral peptide delivery by varying ratio of polymers. The use of bioerodible and biodegradable polymers for the drug delivery is enabling it for the safe delivery of the active material. As these porous systems have also been studied for the drug delivery through pulmonary route which shows that these system can show effective drug release even in the scarce of the dissolution fluid thus colon is an effective site for targeting for drug release. These carriers also require to be developed for alternative drug administration routes like parenteral and pulmonary route. These particles can also be used as the cell culture media and thus can also be employed for stem cell culture and cellular regenaration in the body. Due to their elegance, these carrier systems have also found their application in cosmetics. These characteristic features of porous microspheres motivated the researchers to develop other such particles including nanosponges, nanoferrosponges and porous microbeads. These developments enabled researchers to utilize them variably. These novelties in formulation also open new ways for drug delivery.

12. Conclusion

This study presented the MDS which were developed for topical drug delivery as a carrier for controlled oral drug delivery. Various researchers have explained the potential of microsponges for targeting the drug molecule to the various parts of GIT including ascending colon and stomach. This review also revealed that microsponges need extensive research for the proper development of this technology as this system has a vast scope for development and commercial utilization as a large field is left unexplored. This carrier system also helped in increasing the stability of drug in formulation. The real challenge of MDS in future is the development of the delivery system for the oral peptide delivery by varying ratio of polymers. But the use of bioerodible and biodegradable polymers for the drug delivery is enabling it for the safe delivery of the active material.

13. Expert opinion

Controlled drug delivery systems comprising microsponges hold the potential to reduce the dosing frequency, site-specific delivery, increasing the efficacy of the active compound and improving safety. These microparticulate porous systems with a collapsible structure enable the improved drug entrapment, form a carrier system for chronotherapeutic drug delivery and are easy to formulate. Due to flexibility in fabrication technique, various methods were developed to generate microsponges. Various advantages associated with microsponges generate promising potential for their application in oral drug delivery. The microsponges are free flowing and have better compressibility, thus may be effectively converted to solid oral dosage form. Their resilient character leads them to the plastic deformation during compression resulting in the mechanically strong tablet.

Irrespective of their various advantages and research attempts these carrier particles are still suffering from a non-commercial utilization for oral drug delivery because a suitable pilot plant scale-up attempt for this purpose was not made. Various researchers have successfully studied their potential for oral drug delivery specifically for colon

targeting but with little modification microsponges can also be used as multiparticulate gastroretentive carrier particles. Due to their attributes, these particles specifically bind to the luminal rough surface of the targeted site and provide local retention of active ingredient that can treat localized diseases more efficiently. These properties of microsponges make them a suitable carrier for the treatment of localized diseases like colonic infection, inflammatory bowel disease and colorectal cancer. These particles also hold the promise for sustained drug release thus can be used for clinical treatment of various diseases.

Various attempts to study the biopharmaceutical advantages of microsponges revealed that these particles can increase the drug dissolution rate and bioavailability of various active ingredients that may help in quick achievement and maintenance of effective concentration. These carriers also hold the potential of effective protein delivery to the targeted site. Along with their advantages microsponges also have some disadvantages and researchers are making efforts to overcome or utilize these limitations in other ways.

Microsponges due to their unique characteristic features hold promising opportunities in the development of various novel pharmaceutical applications for oral drug delivery in the upcoming years. New classes of pharmaceuticals, biopharmaceuticals (peptides, proteins and DNA-based therapeutics) are fueling the rapid evolution of drug delivery technology. Thus, MDS is a very rapidly emerging field which is needed to be explored.

Due to their aesthetic physical properties and better control on drug release, microsponges can be used as a carrier particles in a solid dosage form to hold the active ingredients in a protected environment and provide controlled delivery of oral medication to the targeted site of GIT, where the drug will be released on exposure to specific enzymes in the colon. Studies proved that colon-targeted systems comprising microsponges provide chronotherapeutic drug release thus can be used for treatment of circadian diseases. This approach if successfully utilized should open up exclusively novel opportunities for microsponge-based drug delivery system.

Declaration of interest

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